REMARKS

A check for $690 for the requisite fee for a three-month extension of time ($510) and the fee for filing a supplemental Information Disclosure Statement ($180) accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application during its pendency may be charged to Deposit Account No. 06-1050. If a Petition for Extension of time is needed, this paper is to be considered such Petition.

The specification is amended herein to update the priority document information. The specification also is amended herein to comply with the sequence rules 37 C.F.R. §1.821(d) by inserting the sequence identification numbers of the MTSP protein sequences shown in Figure 4. The amendment finds basis in the specification, for example, at page 10, line 23 through page 11, line 1 in which the sequence identification numbers of the exemplary MTSP proteins are identified. No new matter has been added.

Claims 1-3, 5-7, 9-14, 16, 18-20, 34-36, 40-46, 48-57, 72-75, 91, 108, 109, 113-116, 118-120, 122-129 and 137 are pending in this application. Claims 1, 10, 12, 14, 16-20, 35 and 42 are amended herein. Claims 4, 8 and 17 are cancelled herein without prejudice or disclaimer. Claim 137 is added. Claim 1 is amended herein to more clearly point out that the claimed polypeptides include only an MTSP protease domain or a smaller portion of the protease domain with catalytic activity but do not include additional MTSP regions. The amended claim also specifies that the MTSP portion of the polypeptide has serine protease activity. Claim 1 also is amended to correct a minor typographical error. Basis for the amendments can be found at 31, lines 1-5 and at page 25, lines 16-21. Claims 10 and 12 are amended to provide consistent language with claim 1. Basis for the amendment can be found, for example, at page 8, lines 15-21, page 25, lines 22-27 and in the claims as originally filed. Claim 14 is amended to provide consistent language with claim 1 on which it depends. Basis for the amendment can be found for example, at page 52, lines 3-25 and in claim 14 as filed.

Claims 16-20 are amended to more distinctly claim the subject matter by replacing the recitation "mutein" with –polypeptide–. Basis for the amendment can be found throughout the specification (for example, see page 10, lines 3-13). Claims 16 and 18 are also amended to more distinctly claim the subject matter by replacing the recitation "unmutated" with –unmodified–. Basis for the amendment can be found throughout the specification (for example, see page 77, line 16 through page 79, line 21).

Claim 16 is further amended to more distinctly claim the subject matter by providing consistent claim language with claim 1. Additionally, the amendment clarifies that the claimed polypeptides are directed to those that include a catalytic triad. Basis for the amendment can be found throughout the specification (for example, see page 26, lines 13-21). Claim 16 is also amended to recite up to about 60% of the amino acids of the MTSP portion of the polypeptide are replaced with another amino acid. Basis for the amendment is found throughout the specification (for example, see page 10, lines 3-13; page 26, lines 26-28; and the original claims as filed). Claim 16 is further amended to recite that the polypeptide has serine protease activity on the particular listed substrates. Basis for the amendment can be found throughout the specification (for example, see page 179, line 15 to page 180, line 8).

Claim 35 is amended to maintain consistent claim language by replacing the recitation "protein" with –polypeptide–. Additionally, claim 35 is amended to specify that the conjugate retains serine protease activity. Basis for the amendment can be found for example, at page 123, line 30 to page 124, line 7. Claim 42 is amended to depend from claim 41 and to recite that the array includes polypeptides having different MTSP protease domains. Basis for this amendment can be found at page 132, lines 4-8 and in the claim as originally filed.

Claim 137 is added. Basis for this claim can be found at page 25, lines 8-15; page 179, line 15 through page 180, line 8; and page 26, lines 13-21. No new matter is added.

I. OBJECTION TO CLAIMS 11-14 AND 34 AS ALLEGEDLY DIRECTED TO NON-ELECTED SUBJECT MATTER

Claims 11-14 and 34 are objected to for allegedly being drawn to non-elected subject matter. In the previous response, applicant elected, with traverse, Group 1, directed to claims 1-14, 16-20, 34-36, 40-42, 56, 57, 72-75, 91, 108, 109, 113, 114 and 127-129, and elected as a species for search purposes MTSP1. Claims 11-14 and 34 are included in elected Group 1, and claims 11-14 and 34 read on the elected species. Hence, claims 11-14 and 34 are directed to elected subject matter.

II. REJECTION OF CLAIM 4 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - Written Description

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as allegedly including subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had

possession of the claimed subject matter. The Examiner states that there is an adequate written description of a genus of polypeptides having proteolytic activity of a serine protease domain. Claim 4 is rejected because it is alleged that the specification fails to define those structural features of SEQ ID NO:2 that are commonly possessed by member of the "human genus" that distinguish them from other "non-human" polypeptides.

Without conceding the propriety of this rejection, it is respectfully submitted that this rejection is rendered moot by the cancellation of claim 4 herein.

III. REJECTION OF CLAIMS 1-9, 11, 16-20, 34-36 AND 40-42 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - Written Description

Claims 1-9, 11, 16-20, 34-36 and 40-42 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed subject matter. The Examiner states that the claims are directed to a genus of polypeptides that include a protease domain or catalytically active portion thereof of a type-II membrane-type serine protease (MTSP) from any source. The Examiner alleges that there is insufficient written description because the specification allegedly teaches only one species, the polypeptide having the amino acid sequence of SEQ ID NO:50. The Examiner contends that the disclosure of one species is not enough to describe the whole genus, and alleges that there is no evidence on record of the relationship between the structure of the serine protease domain of SEQ ID NO:50 and the structure of a catalytically active portion of an MTSP polypeptide.

This rejection is respectfully traversed.

RELEVANT LAW

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject mater at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of

> the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989). The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987).

A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

THE CLAIMS

Claim 1 is directed to a substantially purified single-chain polypeptide that includes an MTSP portion. The MTSP portion is a protease domain of a type-II membrane-type serine protease (MTSP) or a catalytically active portion of the MTSP protease domain. The MTSP portion also is the only portion of the polypeptide from an MTSP and the MTSP portion of the polypeptide has serine protease activity. Hence, the claimed polypeptides only include from an MTSP a protease domain or a smaller catalytically active fragment of the protease domain; no other MTSP sequences are included. Claim 2-9, 11, 16-20 and 34 depend from claim 1 and are directed to various embodiments including where the MTSP is not expressed on endothelial cells, where the MTSP is expressed in tumor cells at particular levels and where the polypeptide retains particular features of an MTSP. Claims 35 and 36 depend from claim 1 and are directed to a conjugate including a protein of claim 1, and a targeting agent linked to the protein directly or via a linker. Claims 40-42 are directed to a solid support including two or more polypeptides of claim 1 linked thereto either directly or via a linker.

ANALYSIS

In this instance, there is no basis to conclude that a person skilled in the art at the time the application was filed would not recognize in the applicant's disclosure a description of the invention defined by the claims. The Examiner alleges that the specification discloses SEQ ID NO:50 as the only species of the claimed genus, and alleges that such a disclosure is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus.

Applicant respectfully disagrees. Applying the guidelines for a written description analysis of claims directed to a genus reveals that the written description requirement is satisfied. The analysis for compliance with the written description requirement where claims are directed to a genus is as follows:

a) does the art indicate substantial variation among the species within the genus?

b) are there a representative number of examples explicitly or implicitly disclosed in the application as determined by assessing whether the skilled artisan would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species?

The Claimed Genus

As discussed above and below, claim 1 is directed to a substantially purified single-chain polypeptide that includes an MTSP portion that is a protease domain of a type-II membrane-type serine protease (MTSP) or a catalytically active portion thereof, where the MTSP portion is the only portion of the polypeptide from an MTSP and has serine protease activity. Thus, the MTSP portion represents a genus that encompasses the exemplified species and other species that are similar in function to the exemplified species.

A. No Substantial Variation Among the Species

The specification teaches that those of skill in the art recognize common elements among MTSPs and the protease domains of MTSPs, and the specification teaches a number of conserved characteristics for MTSPs. For example, see page 49, lines 3-15, which discloses:

> The MTSPs are a family of transmembrane serine proteases that are found in mammals and also other species that share a number of common structural features including: a proteolytic extracellular C-terminal domain; a transmembrane domain, with a hydrophobic domain near the N-terminus; a short cytoplasmic domain; and a variable length stem region containing modular domains. The proteolytic domains share sequence homology including conserved his, asp, and ser residues necessary for catalytic activity that are present in conserved motifs. The MTSPs are

> synthesized as zymogens, and activated to double chain forms by cleavage. It is shown herein that the single chain proteolytic domain can function *in vitro* and, hence is useful in *in vitro* assays for identifying agents that modulate the activity of members of this family. Also provided are family members designated MTSP3, MTSP4 and an MTSP6 variant.

The specification provides additional structural and functional characteristics of the various MTSPs. For example, the specification teaches that the MTSP family of proteases include a serine residue that is involved in the hydrolysis of proteins or peptides. The serine residue can be part of the catalytic triad mechanism, which includes a serine, a histidine and an aspartic acid in the catalysis, or can be part of the hydroxyl/ε-amine or hydroxyl/α-amine catalytic dyad mechanism, which involves a serine and a lysine in the catalysis (for example, see page 17, lines 24-30). Further the specification teaches, for example at page 19, lines 3-24, that:

> Exemplary MTSP proteins, with the protease domains indicated, are illustrated in Figures 1-3. Smaller portions thereof that retain protease activity are contemplated. The protease domains vary in size and constitution, including insertions and deletions in surface loops. They retain conserved structure, including at least one of the active site triad, primary specificity pocket, oxyanion hole and/or other features of serine protease domains of proteases. Thus, for purposes herein, the protease domain is a portion of a MTSP, as defined herein, and is homologous to a domain of other MTSPs, such as corin, enterpeptidase, human airway trypsin-like protease (HAT), MTSP1, TMPRSS2, and TMPRSS4, which have been previously identified; it was not recognized, however, that an isolated single chain form of the protease domain could function proteolytically in *in vitro* assays. As with the larger class of enzymes of the chymotrypsin (S1) fold (see, e.g., Internet accessible MEROPS data base), the MTSPs protease domains share a high degree of amino acid sequence identity. The His, Asp and Ser residues necessary for activity are present in conserved motifs. The activation site, which results in the N-terminus of second chain in the two chain forms is has a conserved motif and readily can be identified (see, e.g., amino acids 801-806, SEQ ID No. 62, amino acids 406-410, SEQ ID No. 64; amino acids 186-190, SEQ ID No. 66; amino acids 161-166, SEQ ID No. 68; amino acids 255-259, SEQ ID No. 70; amino acids 190-194, SEQ ID No. 72).

The specification also directs those skilled in the art to exemplary art that describes common structural features shared by the transmembrane serine proteases (for example, see page 18, lines 1-15). Thus, the art recognizes that there are common conserved elements among MTSPs.

B. Representative Number of Species

An adequate written description for a claimed genus need only provide "relevant, identifying characteristics" of a representative number of species (MPEP §2163). The

specification provides a representative number of examples explicitly and implicitly.

For example, the disclosure on pages 9-10 recites:

> Other MTSP protease domains of interest herein, particularly for use in *in vitro* drug screening proteolytic assays, include, but are not limited to: corin (accession nos. AF133845 and AB013874; see, Yan *et al.* (1999) J. Biol. Chem. 274:14926-14938; Tomia et al. (1998) J. Biochem. 124:784-789; Uan *et al.* (2000) Proc. Natl. Acad. Sci. U.S.A. 97:8525-8529; SEQ ID Nos. 61 and 62 for the human protein); enteropeptidase (also designated enterokinase; accession no. U09860 for the human protein; see, Kitamoto *et al.* (1995) Biochem. 27: 4562-4568; Yahagi et al. (1996) Biochem. Biophys. Res. Commun. 219:806-812; Kitamoto *et al.* (1994) Proc. Natl. Acad. Sci. U.S.A. 91:7588-7592; Matsushima *et al.* (1994) J. Biol. Chem. 269:19976-19982; see SEQ ID Nos. 63 and 64 for the human protein); human airway trypsin-like protease (HAT; accession no. AB002134; see Yamaoka *et al.* J. Biol. Chem. 273:11894-11901; SEQ ID Nos. 65 and 66 for the human protein); hepsin (see, accession nos. M18930, AF030065, X70900; Leytus et al. (1988) Biochem. 27: 11895-11901; Vu *et al.* (1997) J. Biol. Chem. 272:31315-31320; and Farley *et al.* (1993) Biochem. Biophys. Acta 1173:350-352; SEQ ID Nos. 67 and 68 for the human protein); TMPRS2 (see, Accession Nos. U75329 and AF113596; Paoloni-Giacobino *et al.* (1997) Genomics 44:309-320; and Jacquinet *et al.* (2000) FEBS Lett. 468: 93-100; SEQ ID Nos. 69 and 70 for the human protein) TMPRSS4 (see, Accession No. NM 016425; Wallrapp *et al.* (2000) Cancer 60:2602-2606; SEQ ID Nos. 71 and 72 for the human protein); and TADG-12 (also designated MTSP6, see SEQ ID Nos. 11 and 12; see International PCT application No. WO 00/52044, which claims priority to U.S. application Serial No. 09/261,416).

The specification also includes specific sequences for exemplary MTSPs. For example, see page 52, lines 12-31 which recites:

> Specific sequences for the following human MTSPs and domains thereof are provided as follows: SEQ ID No. 3 MTSP3 nucleic acid sequence; SEQ ID No. 4 MTSP3 amino acid sequence; SEQ ID No. 5 MTSP4 nucleic acid encoding the protease domain; SEQ ID No. 6 MTSP4 amino acid sequence of the protease domain; SEQ ID No. 7 MTSP4-L nucleic acid sequence; SEQ ID No. 8 MTSP4-L amino acid sequence; SEQ ID No. 9 MTSP4-S nucleic acid sequence; SEQ ID No. 10 MTSP4-S amino acid sequence; SEQ ID No. 11 MTSP6 nucleic acid sequence; SEQ ID No. 12 MTSP6 amino acid sequence. SEQ ID No. 1 sets forth the nucleic acid sequence of the long form of MTSP1; SEQ ID No. 2 the encoded amino acid sequence; SEQ ID No. 49 sets forth the sequence of a protease domain of an MTSP1, and SEQ ID No. 50 the sequence of the encoded single chain protease domain thereof. Figures 1-3 depict the structural organization of the MTSP3, MTSP4 and MTSP6, respectively.
>
> In particular, exemplary protease domains include at least a sufficient portion of sequences of amino acids set forth as amino acids 615-855 in SEQ ID No. 2 (encoded by nucleotides 1865-2587 in SEQ ID No. 1; see also SEQ ID Nos. 49 and 50) from MTSP1 (matriptase), amino acids 205-437 of SEQ ID NO. 4 from

> MTSP3, SEQ ID No. 6, which sets forth the protease domain of MTSP4, and amino acids 217-443 of SEQ ID No. 11 from MTSP6.

Hence, the specification explicitly discloses several proteases by family (matriptase, corin, enteropeptidase, human airway trypsin-like protease, hepsin, TMPRS2, TMPRSS4 and TADG-12) and provides specific nucleic acid sequences and amino acid sequences for exemplary species. Thus, the specification describes more than a single representative species as alleged by the Examiner.

The specification states that the claimed single-chain polypeptide includes an MTSP protease domain or catalytically active portion thereof that can be from any MTSP family, for example from a mammal, including human MTSP. For example, see page 8, line 30 through page 9, line 8, which recites:

> The protease domains provided herein include, but are not limited to, the single chain region having an N-terminus at the cleavage site for activation of the zymogen, through the C-terminus, or C-terminal truncated portions thereof that exhibit proteolytic activity as a single-chain polypeptide in *in vitro* proteolysis assays, of any MTSP family member, preferably from a mammal, including and most preferably human, that, for example, is expressed in tumor cells at different levels from non-tumor cells, and that is not expressed on an endothelial cell. These include, but are not limited to : MTSP1 (or matriptase), MTSP3, MTSP4 and MTSP6.

The specification provides a number of methods for identification, production, isolation, synthesis and/or purification of MTSPs. The specification states, for example, that MTSP3, MTSP4 and MTSP6 are isolated from any animal, particularly a mammal, and includes but are not limited to, humans, rodents, fowl, ruminants and other animals (see page 20, lines 21-23; page 21, lines 11-13; and page 21, lines 29-31, respectively). Alternative methods for obtaining the MTSP protein than by directly isolating the MTSP protein are also provided. These include synthesis using genomic DNA, chemically synthesizing the gene sequence from a known sequence and making cDNA to the mRNA that encodes the MTSP protein, for example, and inserting the isolated nucleic acids into an appropriate cloning vector (for example, see pages 67-79).

The instant specification clearly describes structurally and functionally known MTSPs. The catalytic function of MTSPs is known in this art. The catalytically active purified single-chain form polypeptide including the protease domain of type II MTSPs or catalytically active portions thereof described in the instant application elicit their effect through these known functions of the protease domains of MTSPs. The activity of the claimed substantially purified single-chain polypeptide including the protease domain of a

MTSP or a catalytically active portion thereof is described and demonstrated for the exemplary polypeptides.

Thus, the specification clearly describes and identifies various MTSPs, provides a list of exemplary MTSPs and directs the skilled artisan to several references describing exemplary MTSP protease domains. The specification provides a written description for structural and functional characteristics of the various MTSPs and thus provides "relevant, identifying characteristics" for the species of the genus. The specification exemplifies isolation or preparation of MTSPs, including methods known to those skilled in this art. Accordingly, applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the disclosed species so that the skilled artisan would recognize that applicant "had possession" of the genus as claimed at the time of filing of the original application.

IV. REJECTION OF CLAIMS 11-9, 11, 16-20, 34-36 AND 40-42UNDER 35 U.S.C. §112, FIRST PARAGRAPH – Scope of Enablement

Claims 1-9, 11, 16-20, 34-36 and 40-42 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to describe the claimed subject matter in such a way as to enable one skilled in the art to make and use the claimed subject matter commensurate in scope with these claims. The Examiner states that the specification is enabling for a polypeptide that includes amino acids 615-855 of SEQ ID NO:2 or the polypeptide of SEQ ID NO:50. The Examiner alleges that the specification does not reasonably provide enablement for a polypeptide that includes any protease domain of any type II membrane type serine protease or catalytically portion thereof that include polypeptides with a modification of 90-95% and having a free cysteine replaced with a serine or a polypeptide with a protease domain having 40-95% sequence identity to amino acids 615-855 of SEQ ID NO:2. It is alleged that it would require undue experimentation for one of skill in the art to make such modified polypeptides with an expectation of success because the result of such modifications in unpredictable.

This rejection is respectfully traversed.

RELEVANT LAW

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon

a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims (i.e. the "Forman factors"). *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. The focus of the inquiry is whether everything within the scope of the claim is enabled. As concerns the breadth of a claim relevant to enablement, the only concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

It is incumbent upon the Examiner to first establish a *prima facie* case of non-enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369-70 (CCPA 1971). The requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

> ... we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim ... What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

The law is clear that patent documents need not include subject matter that is known in the field of the invention and is in the prior art, for patents are written for persons

experienced in the field of the invention. See *Vivid Technologies, Inc. v. American Science and Engineering, Inc.*, 200 F.3d 795, 804, 53 USPQ2d 1289, 1295 (Fed. Cir. 1999) ("patents are written by and for skilled artisans"). To hold otherwise would require every patent document to include a technical treatise for the unskilled reader. Although an accommodation to the "common experience" of lay persons may be feasible, it is an unnecessary burden for inventors and has long been rejected as a requirement of patent disclosures. See *Atmel Corp.*, 198 F.3d at 1382, 53 USPQ2d at 1230 (Fed. Cir. 1999) ("The specification would be of enormous and unnecessary length if one had to literally reinvent and describe the wheel."); *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983) ("Patents are written to enable those skilled in the art to practice the invention, not the public.")

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. The "invention" referred to in the enablement requirement of section 112 is the claimed subject matter. *Lindemann Maschinen-fabrik v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with evidence or reasoning which is inconsistent with the contested statement.

Id. (emphasis in original); *See also Fiers v. Revel*, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993);, *Gould v. Mossinghoff*, 229 USPQ 1, 13 (D.D.C. 1985), *aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg*, 822 F.2d 1074, 3 USPQ2d 1302 ("there is no requirement in 35 U.S.C. § 112 or anywhere else in patent law that a specification convince persons skilled in the art that the assertions in the specification are correct"). A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987).

PTO GUIDELINES

The PTO has promulgated guidelines, which incorporate the above-noted law, for examining chemical/biotechnical applications with respect to 35 U.S.C. §112, first paragraph, enablement. As set forth in the guidelines, the standard for determining whether the specification meets the enablement requirement is whether it enables any person skilled in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988). In determining whether any experimentation is "undue," consideration must be given to the above-noted factors.

As indicated in the published guidelines, it is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The analysis must consider all the evidence related to each of the factors, and any conclusion of non-enablement must be based on the evidence as a whole. *Id.* 8 USPQ2d at 1404 & 1407.

ANALYSIS

Application of the Factors Enumerated in In re Wands

As discussed in detailed below, a consideration of the factors enumerated in In re Wands demonstrates that the application, in conjunction with what was known to one of skill in the art, teaches how to make and use the subject matter as claimed without undue experimentation.

Breadth of the Claims

Claim 1 is directed to a single chain polypeptide that includes an MTSP portion that is a protease domain of an MTSP or a catalytically active portion of an MTSP protease domain. The MTSP portion is the only portion of the single-chain polypeptide from an MTSP and it has serine protease activity. Dependent claims 2-9 are described above and are directed to polypeptides where the MTSP is not expressed on endothelial cells and where the MTSP is expressed in tumor cells at particular levels.

Claims 13-14 and 16-20 depend from claim 1. These claims are directed to MTSP polypeptides that include modifications of the exemplified MTSP sequences. For example, the polypeptides of claim 13 incorporate the features of claim 1 and in addition have at least about 40%, 60%, 80%, 90% or 95% sequence identity with the exemplified MTSP1, MTSP3, MTSP4 and MTSP6 protease domain sequences as set forth in the claim. Claim 14 is directed to polypeptides with the features of claim 1 that are encoded by nucleic acid molecules that hybridize under high stringency to MTSP-encoding nucleic acid molecules. Claim 16 is directed to polypeptides of claim 1 that include an active site triad and that retain at least 10% catalytic activity on the specified substrates. Claims 17-20, dependent on claim 16, specify additional features of such polypeptides including catalytic activity and sequence identity features. Claim 34 is directed to polypeptides of claim 1 where the MTSP portion is selected from the listed polypeptides.

Claims 35 and 36 depend from claim 1 and are directed to a conjugate including a protein of claim 1, and a targeting agent linked to the protein directly or via a linker. Claims 40-42 are directed to a solid support including two or more polypeptides of claim 1 linked thereto either directly or via a linker.

Level of Skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Teachings of the Specification

The specification teaches the structural and functional features sufficient to enable one of skill in the art to make and use the single chain polypeptides including an MTSP portion that is a protease domain or catalytically active portion of an MTSP protease domain, where the MTSP portion is the only portion of the polypeptide from an MTSP and the MTSP portion has serine protease activity. First, the specification teaches that MTSP polypeptides are a family of related serine proteases. For example, page 18, lines 1-23 recites:

> As used herein, "transmembrane serine protease (MTSP)" refers to a family of transmembrane serine proteases that share common structural features as described herein (see, also Hooper et al. (2001) J. Biol. Chem.276:857-860). Thus, reference, for example, to "MTSP" encompasses all proteins encoded by the MTSP gene family, including but are not limited to: MTSP1, MTSP3, MTSP4 and MTSP6, or an equivalent molecule obtained from any other source or that has been prepared synthetically or that exhibits the same activity. Other MTSPs include, but are not

> limited to, corin, enterpeptidase, human airway trypsin-like protease (HAT), MTSP1, TMPRSS2, and TMPRSS4. Sequences of encoding nucleic molecules and the encoded amino acid sequences of exemplary MTSPs and/or domains thereof are set forth in SEQ ID Nos. 1-12, 49, 50 and 61-72. The term also encompass MTSPs with conservative amino acid substitutions that do not substantially alter activity of each member, and also encompasses splice variants thereof. Suitable conservative substitutions of amino acids are known to those of skill in this art and may be made generally without altering the biological activity of the resulting molecule. Of particular interest are MTSPs of mammalian, including human, origin. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson et al. Molecular Biology of the Gene, 4th Edition, 1987, The Bejamin/ Cummings Pub. co., p.224).

The specification teaches that a protease domain from an MTSP polypeptide is active as a single chain polypeptide. Additionally, smaller fragments of the protease domain also are active as single chain polypeptides (page 18, line 24-page 19, line 2):

> As used herein, a "protease domain of an MTSP" refers to the protease domain of MTSP that is located within the extracellular domain of a MTSP and exhibits serine proteolytic activity. It includes at least the smallest fragment thereof that acts catalytically as a single chain form. Hence it is at least the minimal portion of the extracellular domain that exhibits proteolytic activity as assessed by standard assays in vitro assays. Those of skill in this art recognize that such protease domain is the portion of the protease that is structurally equivalent to the trypsin or chymotrypsin fold.

The specification further teaches that MTSP protease domains can vary in sequence but that these proteins retain a conserved structure as well as sequence identity to identified MTSP proteins exemplified in the application. For example, see page 19, lines 3-24, which recites:

> Exemplary MTSP proteins, with the protease domains indicated, are illustrated in Figures 1-3, Smaller portions thereof that retain protease activity are contemplated. The protease domains vary in size and constitution, including insertions and deletions in surface loops. They retain conserved structure, including at least one of the active site triad, primary specificity pocket, oxyanion hole and/or other features of serine protease domains of proteases. Thus, for purposes herein, the protease domain is a portion of a MTSP, as defined herein, and is homologous to a domain of other MTSPs, such as corin, enterpeptidase, human airway trypsin-like protease (HAT), MTSP1, TMPRSS2, and TMPRSS4, which have been previously identified; it was not recognized, however, that an isolated single chain form of the protease domain could function proteolytically in *in vitro* assays. As with the larger class of enzymnes of the chymotrypsin (S1) fold (see, e.g., Internet accessible MEROPS data base), the MTSPs protease domains share a high degree of amino acid sequence identity. The His, Asp and Ser residues necessary for activity are present in conserved motifs. The activation site, which results in the N-terminus of second chain in the two chain forms is has a conserved motif and readily can be identified (see, e.g., amino acids 801-806, SEQ ID No. 62, amino acids 406-410, SEQ ID No. 64; amino acids 186-190, SEQ ID No. 66; amino acids 161-166, SEQ ID No. 68; amino acids 255-259, SEQ ID No. 70; amino acids 190-194, SEQ ID No. 72).

The application describes the protease domain of a number of MTSP family members including MTSP1, MTSP3, MTSP4 and MTSP6. A comparison of sequence identity between the family members (see e.g. Figure 4 of the application) reveals that the protease domains share conserved sequences, including the catalytic triad of His, Asp and Ser residues and their surrounding conserved motifs. Additionally, the specification demonstrates that MTSP protease domains can have a reasonable amount of sequence variation and yet retain serine protease activity. MTSP1, MTSP3, MTSP4 and MTSP6 protease domains share about 40% sequence identity with each other. The specification teaches that each of these protease domains is an example of an MTSP protease domain that has activity in the single chain form.

The specification also teaches additional modifications. For example, see page 26, lines 13-25, which recites:

> Hence smaller portions of the protease domains, particularly the single chain domains, thereof that retain protease activity are contemplated. Such smaller versions will generally be C-terminal truncated versions of the protease domains. The protease domains vary in size and constitution, including insertions and deletions in surface loops. Such domains exhibit conserved structure, including at least one structural feature, such as the active site triad, primary specificity pocket, oxyanion hole and/or other features of serine protease domains of proteases. Thus, for purposes herein, the protease domain is a single chain portion of an MTSP, as defined herein, but is homologous in its structural features and retention of sequence of similarity or homology the protease domain of chymotrypsin or trypsin. Most significantly, the polypeptide will exhibit proteolytic activity as a single chain.

The specification teaches that included in the conserved features of MTSP polypeptides is the catalytic triad. The specification explains that beyond such conserved features the polypeptides are tolerant of modification. The specification explains that such modifications can be effected using numerous methods known in the art. For example, at page77, line 17 through page 78, line 11, the specification states:

> A variety of modifications of the MTSP proteins and domains are contemplated herein. An MTSP-encoding nucleic acid molecule be modified by any of numerous strategies known in the art (Sambrook *et al.*, 1990, Molecular Cloning, A Laboratory Manual, 2d ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, New York). The sequences can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated in vitro. In the production of the gene encoding a domain, derivative or analog of MTSP, care should be taken to ensure that the modified gene retains the original translational reading frame, uninterrupted by translational stop signals, in the gene region where the desired activity is encoded.
>
> Additionally, the MTSP-encoding nucleic acid molecules can be mutated in vitro or in vivo, to create and/or destroy translation, initiation, and/or termination sequences, or to create variations in coding regions and/or form new restriction

> endonuclease sites or destroy pre-existing ones, to facilitate further in vitro modification. Also, as described herein muteins with primary sequence alterations, such as replacements of Cys residues and elimination of glycosylation sites are contemplated. Such mutations may be effected by any technique for mutagenesis known in the art, including, but not limited to, chemical mutagenesis and in vitro site-directed mutagenesis (Hutchinson *et al.*, J. Biol. Chem. 253:6551-6558 (1978)), use of TAB® linkers (Pharmacia). In one embodiment, for example, an MTSP protein or domain thereof is modified to include a fluorescent label. In other specific embodiments, the MTSP protein is modified to have a heterofunctional reagent, such heterofunctional reagents can be used to crosslink the members of the complex.

The specification exemplifies variation in MTSP sequences. For example the specification provides exemplary MTSP1, MTSP3, MTSP4 and MTSP6 sequences. The specification explains that MTSP1 and MTSP3 amino acid sequences have about 43% identity with each other (for example, see page 162, lines 1-2). The specification also discloses that MTSP1 and MTSP4 have about 37% amino acid sequence identity (for example, see page 167, lines 25-29). The specification also teaches that MTSP4 and MTSP6 share about 60% amino acid sequence identity (for example, see page 172, lines 4-9). The specification teaches that each of these MTSP sequences is active in a single chain form that includes the protease domain or a smaller catalytically active portion of the protease domain (see, for example at page 20, lines 1-6). Hence, the specification teaches that MTSP sequences that have between 37%-60% and greater sequence identity are active as single chain polypeptides.

The specification teaches additional modifications of the MTSP polypeptides. For example, the specification explains that for each individual MTSP, the polypeptide sequences can include about 60% amino acid sequence identity with the exemplified MTSP. Such modified polypeptides exhibit serine protease activity as single chain polypeptides. The specification provides exemplary modifications including conservative amino acid substitution (for example, see page 10, lines 3-13) and modifications of cysteine residues and/or of glycosylation sites (for example, see page 78, lines 1-7). The specification also discloses that non-classical amino acids can be introduced as a substitution or addition in the MTSP sequence (for example, see page 79, lines 10-21).

Knowledge of those of skill in the art

At the time of filing of the application and before, those of skill in the art were very familiar with serine proteases generally, including sequence and structure of a number of polypeptide members of the serine protease family. There was a large body of literature directed to serine proteases and there was general understanding of their structures and

requisites for activity. This is evidenced, for example, in the application as filed and in the literature made of record in the submitted Information Disclosure Statements. As noted in the application, a large number of Type II Serine Proteases (TTSPs), also referred to as MTSPs, were known (for example, see pages 4-5). In addition, a large body of knowledge was available for the protein family of serine proteases. (see for example, Hooper *et al. J. Biol. Chem. 276*:857-860, Nienaber *et al.* (2000) *J. Biol. Chem.* 275:7239-48; Sommerhoff *et al.* (1999) *Proc. Natl. Acad. Sci. USA* 96:10984-91; Lu *et al.* (1999) J. Mol. Biol. 292:361-73; Xu *et al.* (2000) *J. Biol. Chem.* 275:378-385, Lin *et al.*(1999) *J. Biol. Chem. 274*: 18231-36 and Bryan (2000) *Biochem. Biophys. Acta 1543*:200-03). These references detail the existing crystal structures, structural comparisons and structural similarities of serine proteases. Hence, a wide variety of structural information on serine proteases was well-known in the art. The references emphasize that the presence of a catalytic triad in the protease confers serine protease activity.

The methods and guidance for comparing amino acid sequences to generate and confirm sequences with sequence identity to an MTSP polypeptide sequence such as SEQ ID NOS: 2 and 50 was available in the art at the time of filing the instant application. As described in the instant specification, computer algorithms such as the "FAST A" program, using for example, the default parameters as in Pearson *et al.* (1988) Proc. Natl. Acad. Sci. USA 85:2444 were available. Other available programs include the GCG program package (Devereux, J., *et al.* , Nucleic Acids Research 12(I):387 (1984)), BLASTP, BLASTN, and FASTA (Atschul *et al.*, J Molec Biol 215:403 (1990); *Guide to Huge Computers*, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo *et al.* (1988) SIAM J Applied Math 48:1073). In addition, methods for generating nucleotide and protein sequence variation were widely available in the art. Thus, one of skill in the art could use such programs with a serine protease sequence, for example, to align the sequence and identify the structural features of importance for retention of activity and use the methods for generating sequence variation to make the identified protein variants.

Methods for assaying protease activity including protease specificity, level of activity and response to inhibitors was well known in the art (see, for example, Lu *et al.* (1999) J. Mol. Biol. 292:361-73; Xu *et al.* (2000) *J. Biol. Chem.* 275:378-385). Methods for high throughput assays and detection were also widely available (See generally, *High Throughput Screening: The Discovery of Bioactive Substance*s (Devlin, Ed.) Marcel Dekker, 1997; Sittampalam *et al., Curr. Opin. Chem. Biol.*, 1:384-91 (1997); and Silverman *et al., Curr.*

Opin. Chem. Biol., 2:397-403 (1998)). Hence, the amount of knowledge of those of skill in the art was extensive and the requisite structural and functional features required for protease activity was well known.

Working Examples

The application provides working examples that demonstrate each of the features of the claimed polypeptides. For instance, the Examples provide detailed guidance on how to isolate MTSP polypeptides that are diverse in sequence. Example 1 describes the cloning of and identification of MTSP3 based on its sequence similarity with MTSP1. Example 2 describes the identification and cloning of two MTSP4 polypeptides, MTSP4-S and MTSP4-L. Example 3 describes the identification and cloning of an MTSP6 polypeptide based on sequence similarity to MTSP4. In each case, an MTSP polypeptide sequence is identified that includes a protease domain with a cleavage site and a catalytic triad (see e.g. Figure 4). As noted, for example, in Example 1, identification of MTSP3 required only 43% sequence identity to identify an MTSP that had the features of the claimed polypeptides. Similarly, Example 2 demonstrates that 37% sequence identity with MTSP1 was sufficient to identify MTSP4.

The Examples demonstrate additional features of the claimed polypeptides. For example, Examples 1, 2, 3 and 6 each demonstrate the expression of MTSP polypeptides in normal and tumor tissues. The working examples further demonstrate that each of the MTSP polypeptides, having, for example, 37-43% sequence identity, is active as a single chain protease domain. For example, Example 1 describes the cloning of MTSP3 into an expression vector and expressing it in *E. coli*. The example describes the purification of the protein and the serine protease activity of the single chain protease domain using a variety of substrates. Examples 4 and 5 describe additional expression vector cloning techniques for *Pichia pastoris* expression for MTSP 3, 4 and 6. Example 5 provides a detailed example of a serine protease assay for the expressed MTSP6 single chain protease domain. Examples 6 and 7 provide a detailed description of the cloning, expression and purification of an MTSP1 single chain protease domain. Example 8 provides detailed serine protease assays for MTSP1. Additionally, Example 1 demonstrates that additional sequence variation can be introduced into single chain protease domains of an MTSP, such as a cysteine to serine change, without altering serine protease activity. Hence, the examples demonstrate the ability of one of skill in the art to isolate and express MTSP single chain polypeptides that include the protease domain without additional regions of MTSP sequence. The examples further demonstrates that one of

skill in the art can identify MTSP sequences with 37-43% sequence identity that share common features of an MTSP and are active as single chain polypeptides.

Predictability

The predictability at issue herein is whether one of skill in the art could predictably make polypeptides that had at least about 40-95% sequence identity with an MTSP1 protease domain, and whether such polypeptides would possess serine protease activity. Applicant respectfully submits that one of skill in the art, given the instant disclosure, could predictably make such polypeptide variants with serine protease activity.

In contrast to the allegations of "unpredictability" set forth in the Office Action, the specification and the knowledge in the art evidence many factors of *predictability* with respect to MTSP polypeptide variants. First, the specification provides exemplary polypeptides. These are defined chemical structures from which one of skill in the art is given a reference point. As explained above, the exemplary polypeptides provided, MTSP1, MTSP3, MTSP4-S, MTSP4-L and MTSP6, share only about 40% sequence identity. The specification demonstrates, however, that these MTSP polypeptides share conserved features including a protease domain with a catalytic triad and N-terminal activation cleavage site. In addition, the specification demonstrates that the protease domain of the MTSP polypeptides possesses serine protease activity as a single chain polypeptide. Hence, the specification provides numerous demonstrations that MTSP polypeptides related by about 40% sequence identity possess the requisite features of the claimed polypeptides.

Second, the specification delineates structural and functional features of the protein. These features identify key regions and residues that one of skill in the art would know to conserve in order to retain serine protease activity. These features also provide reference points for alignments with other known serine proteases. These features also allow one of skill in the art to make further structure-function correlations, again providing predictable correlations of regions and residues to conserve or change. As evidenced by the references cited in the specification and in the Information Disclosure Statements of record in this application, a large body of knowledge pertaining to structure-function relationships of serine proteases was known in the art. In addition, the specification provides exemplary assays to assess serine protease activity, including a variety of substrates for MTSP activity. Additional serine protease assays were available in the art at the time of filing the instant application. One of skill in the art could readily and routinely test any MTSP variant for serine protease activity.

The experimentation necessary to make and use MTSP polypeptides, as described above, is routine. "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. '***The key word is undue, not experimentation.***' " In re Wands, 858 F.2d at 737-38 (quoting In re Angstadt, 537 F.2d at 504; emphasis added; additional internal citations omitted). The art related to serine proteases demonstrates that such experimentation is not undue.

For example, Pearson *et al.* ((1997) *Cabios Invited Review 13(4)*: 325-32) explains that serine proteases share a conserved catalytic site, the catalytic triad. In addition, trypsin-like serine proteases have several diagnostic motifs throughout the protein including a conserved protein fold and anti-parallel β barrels structure that contributes to the function of the protease. Pearson *et al.* states that one could recognize proteins that have protease activity based on these conserved structures. Hence, generation of variants with serine protease activity is routine because one of skill in the art can use such conserved features as a guide for designing the location of variations to maintain these features. In addition, Cheah *et al.* ((1990) *J. Biol. Chem. 265*:7180-7187) provides a demonstration of the predictability of generating variants of serine proteases based on an exemplary sequence. The authors use known structural and functional information about trypsin-like serine proteases to obtain mutations in a rhinovirus 3C protease with predicted functional phenotypes. Thus, the art available at the time of filing and before demonstrates that one of skill in the art could make variants of a serine protease in a predictable manner.

Therefore, one of skill in the art could make and generate variants of MTSP polypeptides with at least about 40-95% identity to the exemplary MTSP7 polypeptide sequences provided in the application. Serine protease activity of these variants could easily and routinely be confirmed using the assays provided in the application and known in the art. The routine manipulations to generate an MTSP variant, *e.g.* selecting non-catalytic triad residues and aligning variant sequences to confirm at least about 40-95% identity, are not unpredictable.

The instant application identifies MTSP polypeptides that possess serine protease activity as a single chain. Such demonstration of single chain activity had not been demonstrated before the instant application. The application provides adequate description to demonstrate that a common feature of MTSP sequences is the activity of a single chain form that includes the protease domain in the absence of other MTSP portions. The application provides exemplary MTSP's that share only about 40% sequence identity and possess such

features. Therefore, the specification demonstrates that by following the teachings of the application, one of skill in the art can predictably identify MTSP polypeptides that possess the claimed characteristics.

Conclusion

In light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, the fact that it is predictable to make variations in MTSP polypeptides and protease domains using the guidance of the specification, and the breadth of the claims, it would not require undue experimentation for one of skill in the art to make and use polypeptides with the features as claimed. Accordingly, a consideration of the factors enumerated above leads to the conclusion that, based on the disclosure in the specification, undue experimentation would not be required to make and use polypeptides as instantly claimed. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection.

Comments with respect to specific points raised in the Office Action

Notwithstanding the arguments above demonstrating that the specification is enabling for the claimed subject matter, Applicant wishes to address specific issues raised in the Office Action.

The instant Office Action alleges that the specification provides only a disclosure of polypeptides set forth as SEQ ID NO:2 and SEQ ID NO:50. Applicant respectfully points out that while the election of species for search purposes is directed to MTSP1, with respect to enablement, the application must be viewed as a whole. The specification details the identification of a set of MTSP polypeptides, related by common structure and serine protease activity as single chain polypeptides. As explained above, the application demonstrates that the family of MTSP polypeptides share common structural and functional features that include single chain forms of the protease domain with serine protease activity. The specification provides examples of polypeptides with 40% sequence identity to MTSP1 that possess these features. These exemplifications must be considered in an examination of enablement.

V. THE REJECTION OF CLAIMS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claim 1 and its Dependent Claims

Claims 1, 2-9, 11-14, 16-20, 34-36 and 40-42 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite, because it is alleged that the claims are unclear whether

the protease domain has any catalytic activity. Claim 1 is amended herein to recite polypeptides that include an MTSP portion where the MTSP portion has serine protease activity. Hence, claim 1 and claims dependent thereon clearly specify the catalytic activity of the claimed polypeptides. Therefore, the rejection as applied to claim 1 and its dependent claims is obviated.

Claims 2 and 3

Claims 2 and 3 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite, because it is alleged that the recited negative limitations are indefinite. It is alleged that it is not clear how one of skill in the art can readily determine such limitations associated with the purified polypeptide. This rejection is respectfully traversed.

As stated in the MPEP:

> "[t]he current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation. So long as the boundaries of the patent protection sought are set forth definitely, albeit negatively, the claim complies with the requirements of 35 U.S.C. 112, second paragraph."

MPEP 2173.05(i). Claims 2 and 3 recite the limitations "wherein the MTSP is not expressed on endothelial cells" and "wherein the MTSP is not expressed on normal endothelial cells *in vivo*." The instant specification clearly delineates such boundaries and details how one of skill ascertains whether or not an MTSP is expressed on particular cells, such as endothelial cells. For example, the specification discloses assays for ascertaining the expression profiles of MTSP polypeptides (for example, see pages 64-66). Assays include the detection of MTSP transcripts in a wide variety of cell types using probes derived from nucleic acid molecules encoding an MTSP. Exemplary MTSP expression profiles using such assays are provided. Additionally, the specification describes the production of MTSP antibodies that can be used to ascertain the expression, localization and quantitation of MTSP polypeptides in samples. Hence, one of skill in the art would be readily able to identify the expression of any particular MTSP on endothelial cells using such methods. Therefore, claims 2 and 3 are definite and comply with the requirements of 35 U.S.C. § 112, second paragraph.

Claims 6-9

Claims 6-9 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite, because it is alleged that it is not clear how one of skill in the art would identify the claimed characteristics. This rejection is respectfully traversed.

Claims 6-9 are directed to polypeptides of claim 1 where the MTSP has particular features of expression and/or activity. Such characteristics include expression and/or activity of the MTSP in tumor cells different from its level of expression and/or activity in non-tumor cells, or where the MTSP is detectable in a body fluid at a level that differs from its level in body fluids in a subject not having a tumor.

The specification explains in detail how one of skill in the art assesses each of these characteristics. For example, at page 64, lines 9-15, the specification describes:

> Each MTSP has a characteristic tissue expression profile; the MTSPs in particular, although not exclusively expressed or activated in tumors, exhibit characteristic tumor tissue expression or activation profiles. In some instances, MTSPs may have different activity in a tumor cell from a non-tumor cell by virtue of a change in a substrate or cofactor therefor or other factor that would alter the apparent or functional activity of the MTSP.

The specification provides examples of differential expression. For instance, the MTSP3 transcript is detected in some forms of lung carcinoma, colon adenocarcinoma and ovarian carcinoma but is not detected in other forms of lung carcinoma, breast carcinoma, pancreatic adenocarcinoma and prostatic adenocarcinoma. The specification also exemplifies a comparison of MTSP4 expression in normal tissues such as liver, heart, colon, and kidney in comparison to expression in tumor cells such as leukemia, Burkitt's lymphomas, colorectal adenocarcinoma and lung carcinoma. The specification also details how one of skill in the art ascertains whether a particular MTSP is expressed differentially in tumor cells versus non-tumor cells. For example, the specification provides an exemplary Northern blot assay for comparing expression of MTSP4 in normal and tumor tissues (e.g., see page 170, line 20 through page 171, line 14). A similar assay is disclosed for comparing expression of MTSP6 in normal and tumor tissues (e.g., see page 175, line 8 through page 176, line 2). With respect to substrate specificity, the specification provides numerous assays for assessing the substrate specificity of an MTSP polypeptide that can be used to assess substrate specificity of MTSP polypeptides in tumor and non-tumor cells. For example, see page 25, lines 10-12; page 80, lines 16-30; page 81, lines 14-23; and page 177, line 11 through page 180, line 16. Therefore, the features specified in claims 6-9 are described in the specification such that one of skill in the art can readily identify such characteristics in the claimed polypeptides.

Claims 35 and 36

Claims 35 and 36 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite because it is alleged that it is unclear whether the conjugates have the same activity

as the polypeptide before conjugation. Applicant respectfully submits that the amendment of claim 35 herein to recite that the conjugate has serine protease activity obviates this rejection.

Claims 40-42

Claims 40-42 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because it is alleged that the phrase "two or more polypeptides" is indefinite. It also is alleged that claim 42 is indefinite in reciting "plurality of different protease domains." The Office Action alleges that it is unclear whether the solid support comprises different MTSP polypeptides having its own protease domain or different protease domains, because claim 40 is limited to polypeptides of claim 1.

Claim 40 is directed to a solid support that includes two or more polypeptides. Applicant respectfully submits that given its plain meaning, the recitation "two or more polypeptides" is clear to one skilled in the art to mean "two polypeptides" or "more than two polypeptides." Thus, the recitation is not indefinite. The polypeptides have the features set forth in claim 1, namely that the polypeptides include an MTSP portion that is a protease domain or a smaller catalytically active portion of the protease domain, that only the MTSP portion of the polypeptide is from an MTSP and the MTSP portion has serine protease activity. Hence, the two or more polypeptides on the support can be the same as each other or different, so long as each polypeptide meets the elements set forth in claim 1.

Claim 42 specifies an embodiment of claim 41, whereby the array includes polypeptides that have different MTSP protease domains. Although the polypeptides of the array have the features as set forth in claim 1, they are not necessarily the same as each other; the array includes polypeptides that have different MTSP protease domains. Therefore, claims 40-42 are definite and comply with the requirements of 35 U.S.C. § 112, second paragraph.

VI. REJECTION OF CLAIMS UNDER 35 U.S.C. §102

A. THE REJECTION OF CLAIMS 1-9, 34-36, 40 AND 41 UNDER 35 U.S.C. §102(a)

Claims 1-9, 34-36, 40 and 41 are rejected under 35 U.S.C. § 102(a) as anticipated by Takeuchi *et al.* (Proc. Natl. Acad. Sci. USA 96: 11054-11061 (1999)) because Takeuchi *et al.* allegedly discloses a serine protease that is 100% identical to amino acids 615-855 of SEQ ID NO:2, is not expressed on endothelial cells, is of human origin, consists essentially of the protease domain having catalytic activity and is expressed on tumor cells. It also is alleged that the reference discloses the polypeptide linked to a his-tag, and on a solid support.

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the "'prior art"' . . . the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). In re Arkey, Eardly, and Long, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

THE CLAIMS

Claim 1 is directed to a single chain polypeptide that includes an MTSP portion that is a protease domain or a catalytically active portion of a protease domain, and that is the only MTSP portion of the polypeptide. The MTSP portion has serine protease activity. Claims 2-9, 34-36, 40 and 41 depend from claim 1 and are directed to various embodiments thereof.

Disclosure of Takeuchi *et al.*

Takeuchi *et al.* discloses a polypeptide that contains 855 amino acids designated as MT-SP1. This protein has sequence identity with the full-length MTSP1 of the instant

application set forth as SEQ ID NO:2. Takeuchi *et al.* discloses a construct that includes amino acids 596-855 of a protein identified therein as MT-SP1 fused to a 10 amino acid His-tag. Takeuchi *et al.* discloses expression of this construct and assays with the expressed protein. The liner sequence of amino acids 596-855 of MT-SP1 disclosed by Takeuchi *et al.* has sequence identity with MTSP1 of the instant application (*e.g.*, SEQ ID NO:2). Takeuchi *et al.* discloses that these proteases exist as precursors that are activated by specific and limited proteolysis (page 11054, left col., first paragraph). Takeuchi *et al.* discloses that under non-denaturing conditions its MT-SP1 His-tagged fusion product refolds and auto-activates by self-cleavage (page 11057, right column, last paragraph). Takeuchi *et al.* discloses that amino acids Cys 604 and Cys 731 are disulfide bonded (see for example, at page 11060, col.1).

Takeuchi *et al.* does not anticipate Claim 1 or any claims dependent thereon

Takeuchi *et al.* does not anticipate any of the instant claims because it fails to disclose any polypeptides that incorporate all of the features of claim 1. Claim 1 is directed to *single chain* polypeptides that have an MTSP portion that is protease domain or a smaller fragment, where the MTSP portion has serine protease activity. Takeuchi *et al.* does not disclose any *single chain* polypeptides that have an MTSP portion as set forth in claim 1 and have serine protease activity. First, the MT-SP1 polypeptide set forth in Figure 1 of Takeuchi *et al.* is not encompassed by the instant claim 1. The disclosed MT-SP1 polypeptide of Takeuchi *et al.* is a full-length protein that includes additional MTSP regions other then a protease domain. Hence, it is not a polypeptide where the only MTSP portion of the polypeptide is a protease domain or a smaller catalytically active portion of the protease domain.

Second, the construct that includes a His-tag and amino acids 596-855 of MT-SP1 is inactive. Takeuchi *et al.* states that the expressed protein must be activated by cleavage before it possesses serine protease activity (see for example page 11057, col.2 – page 11058, col. 1). Since claim 1 specifies that the MTSP portion of the polypeptide has serine protease activity, the polypeptide disclosed by Takeuchi *et al.* does not have all of the features of the polypeptides set forth in claim 1.

Third, the activated protein derived from the expressed His tag-amino acids 596-855 of the MT-SP1 protein disclosed by Takeuchi *et al.* is not a single chain polypeptide. As shown in Figure 3 of the reference, the protease domain is linked to the upstream portion of the polypeptide by a disulfide bond. Takeuchi *et al.* explains that amino acids Cys 604 and Cys 731 are disulfide bonded (see for example, at page 11060, col.1). Thus, the construct

containing amino acids 596-855 includes this disulfide bond. Hence, the protein disclosed by Takeuchi *et al.* is a two-chain polypeptide containing the upstream region with Cys604 disulfide bonded to the protease domain fragment at Cys731.

Further, one of skill in the art would recognize the disclosure of Takeuchi *et al.* to disclose only a two-chain polypeptide that contains the His-tagged protease domain of MT-SP1. Absent the disclosure of the instant application, one of skill in the art recognized MTSP polypeptides only as single chain inactive zymogens which are activated by cleavage to form two-chain activated polypeptides that possess serine protease activity. There was no knowledge in the art that a *single chain* MTSP possessed serine protease activity. In particular, one of skill in the art, absent the disclosure of the instant application, recognized that any protease domain of an MTSP polypeptide was a two chain polypeptide. For example, Lu *et al.* (1999) *J. Biol. Chem.* 272: 31293-300, presents an enteropeptidase polypeptide containing the protease domain of enteropeptidase and additional amino acids upstream of the protease domain (see for example, Fig. 1 at page 31295). As shown in Figure 1 of Lu *et al.*, similar to the protein disclosed by Takeuchi *et al.*, the protease domain is disulfide bonded with amino acids upstream of the protease domain. Lu *et al.* discloses that this protein is a two-chain polypeptide and that in the single chain form was inactive:

> Special attention was paid to the structure of the construct that encodes pro-L-BEK. Several chymotrypsin-like serine proteases have an "extra" disulfide bond that covalently links the activation peptide to the protease domain, and alignment of enteropeptidase with a subfamily of serine proteases suggests that the last cysteine of the heavy chain (Cys-788) is linked to the light chain (Cys-912, or Cys-122 in chymotrypsin-numbering) (5). To preserve this predicted disulfide bond and to avoid the generation of an unpaired or abnormally paired cysteine, the construct retained the carboxyl-terminal 17 amino acids of the heavy chain that correspond to the chymotrypsin activation peptide. Covalent association of the short activation peptide and the catalytic domain was confirmed by demonstrating that under nonreducing conditions, pro-L-BEK and trypsin-activated L-BEK have similar electrophoretic mobility, whereas after reduction, the apparent mass of L-BEK (45 kDa) is substantially smaller than that of pro-L-BEK (60 kDa) (Fig. 2).
>
> Both pro-HL-BEK and pro-L-BEK were purified as single chain proteins and were found to have little (if any) catalytic activity. (page 31298, col. 2).

As evidenced by the publication Lu *et al.*, one of skill in the art at the effective filing date of the instantly claimed subject matter would understand that MTSP serine proteases were inactive as single chain proteins. Takeuchi *et al.* states that its polypeptide fortuitously refolded and auto-activated after re-suspension and purification (page 11060, left column, second full paragraph). Additionally, expression of an MTSP protease domain requires the protein to be in

a two-chain form, with covalent association of the cleaved protease domain and the upstream peptide by disulfide bonding. Takeuchi *et al.* compares characterization of the MT-SP1 protease domain therein to the characterization of the enterokinase domain by Lu *et al.* (see e.g., page 11060, at col.1). Hence, based on the disclosure of Takeushi *et al.* in light of what was known in the art, one of skill in the art would understand the expression of the protease domain of MT-SP1 to be two chain polypeptide with the cleaved protease domain disulfide bonded to the upstream peptide. Therefore, the reference does not disclose any single chain polypeptides that possess serine protease activity.

Anticipation requires that a reference disclose each and every element of a claim. Since Takeuchi *et al.* fails to disclose any single chain polypeptides that include an MTSP portion that is a protease domain of an MTSP or a smaller catalytically active portion where the MTSP portion is the *only* MTSP portion of the polypeptide and the MTSP portion has serine protease activity, Takeuchi *et al.* does not anticipate claim 1 or any claims dependent thereon, including claims 2-9, 34-36 and 40-41.

B. THE REJECTION OF CLAIMS 11-14 and 34 UNDER 35 U.S.C. §102(b)

Claims 11-14 and 34 are rejected under 35 U.S.C. §102(b) as anticipated by Takeuchi *et al.* because it is alleged that the reference discloses a serine protease domain that is 100% identical to amino acids 615-855 of SEQ ID NO:2 where the serine protease domain is identical to the protease domain of SEQ ID NO:2.

Relevant Law

See above.

The Claims

Claims 11-14 and 34 each depend from claim 1 and therefore incorporate the features of claim 1 as described in detail above. Claims 11-14 and 34 are directed to species of polypeptides with particular MTSP portions and with recited identity and/or homology to recited MTSP sequences.

The disclosure of Takeuchi *et al.*

See above.

Analysis

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. As discussed above in detail, Takeuchi *et al.* fails to disclose any *single chain* polypeptides that include an MTSP portion that is a protease domain of an

MTSP or a smaller catalytically active portion where the MTSP portion is the only portion of the single-chain polypeptide from an MTSP and the MTSP portion has serine protease activity. Hence, the reference does not anticipate claim 1. Since claims 11-14 and 34 incorporate all of the limitations of claim 1, Takeuchi *et al.* also does not anticipate any claims dependent on claim 1, including claims 11-14 and 34.

VII. THE REJECTION OF CLAIMS 1-9, 11-14 and 34 UNDER 35 U.S.C. §102(e)/103(a)

Claims 1-9, 11-14 and 34 are rejected under 35 U.S.C. §102(e) as anticipated by O'Brien *et al.* or in the alternative obvious over O'Brien *et al.*, because it is alleged that the reference discloses a polypeptide with 100% identity to full-length MTSP1 as set forth in SEQ ID NO:2 of the instant application. It is further alleged that the polypeptide disclosed by O'Brien *et al.* inherently possess the features set forth in claims 2-3 and 6-9 of the instant application. The Office Action also alleges that the reference discloses a protease domain identified therein as SEQ ID NO:14 that is 100% identical to amino acids 615-855 of SEQ ID NO:2. Hence, the Office Action concludes that the disclosed sequences in O'Brien *et al.* anticipate the claimed subject matter

In the alternative, it is alleged that the claims are obvious over the claimed subject matter because O'Brien *et al.* teaches a method of expressing polypeptides in host cells. It also is alleged that the reference teaches that the protease domain could be released and used as a diagnostic that has the potential for therapeutic intervention. Thus, the Office Action concludes that it would have been obvious to one of skill in the art to express the protease domain disclosed as SEQ ID NO:14 by O'Brien *et al.* and purify the polypeptide. It is alleged that the motivation to make such polypeptides is the disclosed use as a diagnostic for therapeutic intervention. Further, it is alleged that one of ordinary skill in the art would have had a reasonable expectation of success since the expression of heterologous polypeptides was routine in the art and O'Brien *et al.* teaches how to express heterologous polypeptides.

Relevant Law

With respect to anticipation, the relevant law is set out above. Addressing obviousness, in order to set forth a prima facie case of obviousness under 35 U.S.C. § 103:

(1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and

(2) the combination of the cited references must actually teach or suggest the claimed invention.

Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v Montefiore Hosp. 732 F.2d 1572, 1577. 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Under 35 U.S.C. §103, in order to set forth a case of prima facie obviousness, the differences between the teachings in the cited reference must be evaluated in terms of the whole invention, and the prior art must provide a teaching or suggestion to the person of ordinary skill in the art to have made the changes that would produce the claimed product. See, *e.g.*, Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 U.S.P.Q.2d 481, 488 (Fed. Cir. 1984). The mere fact that prior art may be modified to produce the claimed product does not make the modification obvious unless the prior art suggests the desirability of the modification. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, In re Papesh, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

The Claims

Claims 1-9, 11-14 and 34 are described above.

A. THE ANTICIPATION REJECTION

The disclosure of O'Brien *et al.*

O'Brien *et al.* discloses a protein identified therein as TADG-15 with a sequence of amino acids as set forth as SEQ ID NO:2. The reference also discloses a comparison of the amino acid sequence of the protease domain of TADG-15 (SEQ ID NO:14) with other serine protease catalytic domains. O'Brien *et al.* states that TADG-15 can be expressed in host

cells, for example from a construct including SEQ ID NO:1 (the nucleic acid sequence encoding the full-length TADG-15) and/or chemically synthesized. O'Brien *et al.* does not disclose any serine protease activity of TADG-15, nor any assays for serine protease activity of TADG-15.

Analysis

O'Brien *et al.* does not anticipate any of the instant claims. As explained above, claim 1 and claims dependent thereon are not directed to a full-length MTSP polypeptide. The claims are directed to a polypeptide that includes an MTSP protease domain or smaller catalytically active portion thereof but does not include additional MTSP regions. In addition, the claimed polypeptides are single-chain polypeptides and the MTSP portion has serine protease activity. The polypeptides disclosed by O'Brien *et al.* do not possess all of these characteristics.

First, SEQ ID NO:2 disclosed by O'Brien *et al.* is a full-length MTSP. It includes not only a protease domain, but additional MTSP sequences. Hence, it is not a polypeptide where the only MTSP portion is a protease domain or a smaller catalytically active portion of the protease domain as recited in claim 1. Therefore, the disclosure of SEQ ID NO:2 does not anticipate any of the instant claims.

Second, the disclosure by O'Brien *et al.* of SEQ ID NO:14 as a sequence comparison with other serine protease domains is not a disclosure of a substantially purified single chain polypeptide including an MTSP portion as recited in claim 1 that possesses serine protease activity. A reference must contain an enabling disclosure to be an anticipatory reference. "One of ordinary skill in the art must be able to make or synthesize" the composition. (see MPEP 2121.02). Where a process is not available for making the composition at the time of the disclosure, mere naming without more is not sufficient. MPEP 2121.02 citing *In re Hoeksema*, 399 F.2d 269. O'Brien *et al.*, absent the disclosure of the instant application, is not an enabling reference for a substantially purified *single chain* polypeptide that includes an MTSP protease domain without other MTSP portions and that has serine protease activity. O'Brien *et al.* does not disclose the expression of SEQ ID NO:14, nor any protease activity.

As discussed above, until the disclosure of the instant application, one of skill in the art understood MTSP serine proteases to be active only as *two chain* polypeptides. For example, Lu *et al.* (1999) *J. Biol. Chem.* 272: 31293-300, discloses that single chain MTSP polypeptide is inactive. Cleavage of the MTSP and production of a two chain polypeptide where the protease domain is covalently bonded to the upstream polypeptide sequence by a

disulfide bond creates an active serine protease. Additionally, as evidenced by the publications of Lu *et al.*, expression of a polypeptide containing the protease domain is only active following activation cleavage and the creation of a two chain polypeptide. Hence, one of skill in the art, in light of the knowledge of the art, would view O'Brien *et al.* as disclosing a polypeptide sequence without disclosure of how to make such polypeptide as a single chain that possessed serine protease activity. Therefore, O'Brien *et al.* is not an enabling reference and it does not anticipate any of the claimed subject matter.

B. THE OBVIOUSNESS REJECTION

Differences Between the Claims and the Teachings of O'Brien *et al.*

As explained above, O'Brien *et al.* teaches a protein identified therein as TADG-15 with a sequence of amino acids as set forth as SEQ ID NO:2. The reference teaches only the expression of the full-length TADG-15 in host cells. The reference does not provide any teaching or suggestion of any forms of TADG-15 that possess serine protease activity. The reference provides the linear amino acid sequence of SEQ ID NO:14 containing the protease domain of TADG-15, but the reference provides no teaching or suggestion of how one of skill in the art could generate a single chain polypeptide containing such sequence that possesses serine protease activity.

Analysis

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following:

The teachings of O'Brien *et al.* do not result in the instantly claimed compositions.

As explained above, claim 1 is directed to polypeptides including an MTSP portion that is a protease domain or a smaller catalytically active portion thereof, where the MTSP portion is the only part of the polypeptide from an MTSP, where the polypeptide is a single chain and where the MTSP portion has serine protease activity. O'Brien *et al.* fails to teach or suggest polypeptides that include all of these features.

O'Brien *et al.* teaches a full-length TADG-15 polypeptide. TADG-15 shares sequence identity with MTSP1; hence TADG-15 (SEQ ID NO:2 of O'Brien *et al.*) is not a polypeptide where the protease domain or a smaller portion of the protease domain is the only MTSP portion of the polypeptide. Further, there is no teaching or suggestion of smaller fragments of TADG-15 that are single chain polypeptides and that retain serine protease activity. The smaller fragments of TADG-15 taught by O'Brien *et al.* are small antigenic

fragments, of from 10-50 residues, that have only the property of binding to a TADG-15-specific antibody (see, for example at col.9, lines 22-39). There is no teaching or suggestion that the fragments of TADG-15 retain catalytic activity.

Additionally, although O'Brien *et al.* teaches a linear sequence of amino acids set forth as SEQ ID NO:14 including the protease domain of TADG-15, it does not teach how to make a single chain polypeptide that has serine protease activity. The application does not teach or suggest any expression of SEQ ID NO:14. Nor does it teach or suggest how to make a polypeptide including such as sequence as an active single chain. Although the Office Action alleges that one of ordinary skill in the art could routinely express heterologous proteins and therefore would have had a reasonable expectation of success to express the protease domain, the art evidences that the opposite is true.

As discussed above, at the time of filing the instant application, one of skill in the art, recognized that any protease domain of an MTSP polypeptide was a two chain polypeptide (for example, see Lu *et al.* (1999) *J. Biol. Chem.* 272: 31293-300). The literature at the time of filing the instant application disclosed that MTSP serine proteases are synthesized as inactive single chain zymogens that are activated to double chain forms by cleavage.

Hence, in the absence of the instant application, the art at the time of filing evidenced that single chain serine protease polypeptides were inactive. Further, the only polypeptides that contained serine protease domains in isolation from other regions of the protein were two-chain polypeptides. As explained by Lu *et al.*, such two-chain structure was assumed to be critical for serine protease function. Hence, without further teachings specifically for the generation of a single chain polypeptide that possesses serine protease activity, O'Brien *et al.* does not teach or suggest the polypeptides of claim 1. Claims 2-9, 11-14 and 34 depend from claim 1. Thus, because the teachings of O'Brien *et al.* do not result in the polypeptides as recited in claim 1, claims 2-9, 11-14 and 34 are also nonobvious. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

VIII. THE REJECTION OF CLAIMS 35, 36, 40 AND 41 UNDER 35 U.S.C. §103(a)

Claims 35, 36, 40 and 41 are rejected under 35 U.S.C. § 103(a) as being unpatentable over O'Brien *et al.* (U.S. Patent No. 5,972,616) because O'Brien *et al.* allegedly teaches a polypeptide identified as SEQ ID NO:2 therein with identity to MTSP1 of the instant application. It is alleged that the reference teaches making fragments of SEQ ID NO:2, linking the fragments to a polypeptide and linking such polypeptides to solid supports.

This rejection is respectfully traversed.

Relevant Law

See above.

The Claims

Claims 35 and 36 are directed to conjugates that include polypeptides of claim 1 and a targeting agent. The conjugates have serine protease activity. Claims 40 and 41 are directed to a solid support comprising two or more polypeptides of claim 1.

Analysis

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following:

The teachings of O'Brien *et al.* do not result in the instantly claimed compositions.

Claims 35, 36, 40 and 41 ultimately depend from claim 1. As explained in detail above, O'Brien *et al.* does not teach or suggest a polypeptide that includes an MTSP portion that is a protease domain or a smaller catalytically active portion thereof, where the MTSP portion is the only part of the polypeptide from an MTSP, where the polypeptide is a single chain and where the MTSP portion has serine protease activity. Thus, O'Brien *et al.* does not teach or suggest every element of claim 1. Hence, claim 1 is nonobvious over O'Brien *et al.* and therefore claims 35, 36, 40 and 41, which ultimately depend from claim 1, also are nonobvious over O'Brien *et al.* Applicant respectfully requests that the rejection be withdrawn.

VIII. REJECTION OF CLAIMS 1 AND 16-20 UNDER 35 U.S.C. §103(a)

Claims 1 and 16-20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over O'Brien *et al.* (U.S. Patent No. 5,972,616) and Estell *et al.* in view of Takeuchi *et al.* because it is alleged that O'Brien *et al.* teaches a serine protease domain of an MTSP polypeptide. It further is alleged that it was well known in the art that proteins form disulfide bonds through SH groups of Cys residues. It is alleged that Takeuchi *et al.* teaches that position 731 normally forms a disulfide bond with a Cys residue in the pro-protease domain. The Office Action alleges that Estell *et al.* teaches that Cys residues replaced with Ser residues decrease a polypeptide's susceptibility to oxidation. The Office Action concludes that it would have been obvious to one of ordinary skill in the art to replace a free Cys residue in the protease domain taught by O'Brien *et al.* with a Ser residue in order to enhance stability of the protein. It is alleged that there would have been a reasonable expectation of success because Estell *et al.* teaches that such changes successfully decrease a protein's susceptibility to oxidation.

This rejection is respectfully traversed.

Relevant Law

See related section above.

The Claims

Claim 1 is described above. Claims 16-20 depend from claim 1 and are directed to various embodiments thereof. Claim 16 is directed to polypeptides of claim 1 that include up to about 90% of the amino acids of the MTSP portion of the protein replaced with another amino acid that have an active site triad and the resulting polypeptide is a single chain that has catalytic activity at least 10% of the unmodified polypeptide on a substrate selected from the specified group Claims 17 and 18 further specify additional features of the percentage of replacements and catalytic activity. Claim 19 is directed to polypeptides of claim 16 where a free Cys in the protease domain is replaced with another amino acid and the resulting polypeptide exhibits proteolytic activity. Claim 20 specifies that the free Cys in the protease domain is replaced with a serine.

Differences Between the Claims and the Teachings of the Cited References

O'Brien *et al.* and Takeuchi *et al.*

The teachings of O'Brien *et al.* and Takeuchi *et al.* are discussed above.

Estell *et al.*

Estell *et al.* teaches a method for producing prokaryotic carbonyl hydrolase enzymes, including subtilisin, in recombinant host cells. The method includes introducing mutations into the enzyme sequence including those that exhibit oxidative stability. Amino acids that can be mutated for oxidative stability according to Estell *et al.* include replacing tryptophan, methionine, cysteine and lysine with an amino acid such as alanine or serine.

Analysis

It is respectfully submitted that the Examiner has failed to set forth a case of *prima facie* obviousness because of the following.

The combination of teachings of O'Brien *et al.* with the teachings of Estell *et al.*, and Takeuchi *et al.* does not result in the instantly claimed methods.

As noted above, if an independent claim is non-obvious, then claims dependent thereon are also nonobvious. Combining the teachings of O'Brien *et al.* with the teachings of Estell *et al.*, and Takeuchi *et al.* does not teach or suggest the polypeptides of claim 1, and therefore the combination also does not teach or suggest the polypeptides of claims 16-20, which ultimately depend from claim 1.

As explained in detail above, O'Brien *et al.* does not teach or suggest a single chain polypeptide that includes a MTSP protease domain or smaller portion with catalytic activity, where the polypeptide does not include any additional MTSP portions, and the single chain polypeptide has serine protease activity. O'Brien *et al.* does not teach any polypeptides that have serine protease activity, nor any with particular substrate specificity.

Takeuchi *et al.* does not remedy these defects. Takeuchi *et al.* does not teach a single chain polypeptide that includes an MTSP portion that is the protease domain or a smaller portion thereof that has serine protease activity. Takeuchi *et al.* teaches only full-length MT-SP1 and a *two*-chain activated polypeptide including the protease domain. There is no teaching or suggestion to generate a single chain polypeptide or that such polypeptide would be catalytically active.

Estell *et al.* also fails to remedy the defects of O'Brien *et al.* Estell *et al.* does not teach or suggest any polypeptides that have any MTSP portions. Hence, it does not teach or suggest any of the polypeptides of claim 1. Although Estell *et al.* teaches that cysteine residues can be replaced in prokaryotic carbonyl hydrolase enzymes, there is no teaching or suggestion of how to arrive at the instantly claimed polypeptides with the particular features of claim 1.

O'Brien *et al.*, Takeuchi *et al.* and Estell *et al.*, alone or in any combination, fail to teach polypeptides with the features set forth in claim 1. Therefore, in view of the failure of the references to teach or suggest the polypeptides of claim 1 or the polypeptides of dependent claims 16-20, the combination of references does not render any of the claimed subject matter obvious. Applicant respectfully requests that the rejection be withdrawn.

* * *

In view of the amendments and remarks herein, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

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